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ART UNIT	PAPER NUMBER
1642	

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24

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/512,581	SOTO ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for R ply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 May 2002 and 02 July 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-68* is/are pending in the application.

4a) Of the above claim(s) *3,13-46,50 and 52-67* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-12,47-49 and 51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-68* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☑ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Notice to Comply* .

DETAILED ACTION

1. The amendment filed May 28, 2002 in Paper No. 12 is acknowledged and has been entered. Claims 5, 6, 47-49, and 51 have been amended.

2. The amendment filed January 29, 2003 in Paper No. 16 is acknowledged and has been entered.

3. The amendment filed July 2, 2003 in Paper No. 23 is acknowledged and has been entered. Claims 6-9 have been amended. Claim 68 has been added.

4. Claims 1-68 are pending in the application. As stated in Paper No. 6, claim 3 has been withdrawn from further consideration as being drawn to undisclosed subject matter. Claims 13-46, 50, and 52-67 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected invention, there being no allowable generic or linking claim.

5. Claims 1, 2, 4-12, 47-49, 51, and 68 are currently under prosecution.

Grounds of Objection and Rejection Withdrawn

6. Unless specifically reiterated below, the grounds of objection and rejection set forth in the previous Office action mailed November 26, 2001 (Paper No. 10) have been withdrawn.

For clarity of record, the previous ground of rejection of claim 6 under 35 USC § 112, second paragraph set forth in section 18 of the previous Office action has been withdrawn. The claim is reasonably interpreted to encompass any nucleic acid molecule that initially hybridizes to the nucleic acid molecule of claims 1, 2, 4, or 5 in 6x SSC at about 45°C. Additionally, the previous ground of rejection of claims 47-49 and 51 under 35 USC § 112, second paragraph set forth in section 18 of the previous Office

action has been withdrawn in light of the disclosures at pages 2 and 3, which teach Androgen Shutoff Gene 3 (AS3).

Specification

7. The specification is objected to as failing to comply with the sequence rules set forth under 37 CFR §§ 1.821-1.825 for the reason set forth in the attached Notice to Comply. As noted in the previous Office action, the amino acid sequence encoded by SEQ ID NO: 3, the open reading frame of SEQ ID NO: 1, differs from the amino acid sequence set forth as SEQ ID NO: 2, which the specification teaches is the amino acid sequence encoded by SEQ ID NO: 3. Therefore, the disclosure fails to comply with the requirements set forth under 37 CFR §§ 1.821-1.825 and appropriate correction of the apparent error, or else other satisfactory resolution of the apparent discrepancy is required. It is noted that should the amino acid sequence of SEQ ID NO: 2, as presented in the sequence listing, be incorrect, Applicants can resolve the discrepancy and thereby obviate this ground of objection, by altering the amino acid sequence of SEQ ID NO: 2 to accurately depict the amino acid sequence that is encoded by SEQ ID NO: 3.

8. The disclosure is objected to because of the following informalities: Throughout the specification, the ATCC accession number(s) have been omitted. Appropriate correction is required.

9. The specification is objected to because the use of numerous improperly demarcated trademarks has been noted in this application. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks. See MPEP § 608.01(v).

An example of an improperly demarcated trademark is GenBank™ at page 80.

Appropriate correction of any improperly demarcated trademark is required. Each letter of a trademark should be capitalized or otherwise the trademark should be

demarcated with the appropriate symbol indicating its proprietary nature (e.g., ™, ®), and accompanied by generic terminology. Applicants may identify trademarks using the "Trademark" search engine under "USPTO Search Collections" on the Internet at http://www.uspto.gov/web/menu/search.html.

Claim Rejections - 35 USC § 101

10. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

11. Claim 11 is rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

Claim 11 is drawn to a host cell comprising the expression vector of claim 10. The claims are broadly interpreted to encompass host cells, which are not isolated and are comprised within an organism. Support for this interpretation of the claims can be found in the specification, e.g., at page 6, lines 6-8. Thus, the claims encompass host cells that have been transfected with the expression vector of claim 10, which are comprised within a transgenic animal, including a human.

MPEP § 2105 [R-1] states:

> If the broadest reasonable interpretation of the claimed invention as a whole encompasses a human being, then a rejection under 35 U.S.C. 101 must be made indicating that the claimed invention is directed to nonstatutory subject matter.

12. Claims 1, 2, 4-12, 47-49, 51, and 68 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility, a credible asserted utility, or a well-established utility.

Claims 1, 2, 4-8, and 68 are drawn to an isolated nucleic acid molecule comprising a polynucleotide sequence, or fragment thereof, which is at least 70% identical to the polynucleotide sequence set forth as SEQ ID NO: 1 or SEQ ID NO: 3, or the complement thereof, an isolated nucleic acid molecule encoding a naturally occurring allelic variant of a polypeptide comprising the amino acid sequence set forth as SEQ ID NO: 2, or the complement thereof, an isolated nucleic acid molecule

encoding a polypeptide, or fragment thereof, which comprises an amino acid sequence that is at least 70% identical to the amino acid sequence set forth as SEQ ID NO: 2, or the complement thereof, or an isolated nucleic acid molecule that hybridizes to the nucleic acid molecule of any one of claims 1, 2, 4, or 5. Claims 9-12 and 48 are drawn to a vector comprising the nucleic acid molecule of claim 1, 2, 4, or 5, a host cell transfected with said vector, and a method for producing or obtaining a protein comprising culturing said host cell. Claims 47 and 51 are drawn to kits for diagnosing a disease and determining if a subject is at risk for developing prostate cancer. Claim 49 is drawn to a method for isolating a gene or portion thereof.

The specification discloses that the claimed nucleic acid molecules, vectors, host cells, and methods for obtaining or producing a protein can be used to produce AS3, i.e., the polypeptide of SEQ ID NO: 2, or an allelic variant thereof, or some other protein that is encoded by a nucleic acid molecule that has a polynucleotide sequence, which is either at least 70% identical to the polynucleotide sequence of a polynucleotide sequence encoding AS3 or capable of hybridizing to a nucleic acid molecule comprising such a polynucleotide sequence. The specification discloses that the protein can, for example, be used as immunogen to produce an antibody that binds to the protein; and the antibody can be used, for example, as a reagent to detect the presence of the protein in a biological sample. The specification discloses that the antibody can be used, for example, to isolate the protein to which the antibody binds. In addition, the specification discloses that the claimed nucleic acid molecules can be used probes to determine the presence of a nucleic acid molecule having the a polynucleotide sequence, which is at least partly complementary to the claimed nucleic acid molecule. Alternatively, the specification discloses that the claimed nucleic acid molecules can be used to produce a host cell or a transgenic animal that expresses the nucleic acid molecule. However, none of these utilities meet the requirements set forth under 35 USC § 101, as none of these utilities is specific.

The generic usefulness of a nucleic acid molecule encoding a protein is not disputed, as any nucleic acid molecule can be used, for example, to produce the protein encoded by the nucleic acid molecule. The generic usefulness of the protein encoded

by the nucleic acid molecule is not disputed, because the protein can be used, for example, as immunogen to produce an antibody that binds to the protein. The generic usefulness of an antibody is not disputed, as any antibody can be used, for example, as the specification asserts, to purify the polypeptides to which the antibody binds; nor does the Examiner dispute the generic usefulness of any such antibody in applications designed to monitor the expression of, or detect the polypeptide to which the antibody binds, e.g., Western blot analysis, antibody array analysis, etc. However, because an antibody is generically useful as a such a reagent, the assertion that the claimed antibody can be used as such lacks specificity, because any benefit that might be derived by the public for a grant of a patent monopoly of the existing information disclosed by Applicants' application is not specific to the substance and nature of the claimed antibody. See *Brenner, Comr Pats v. Manson*, 148 USPQ 689 (US SupCt, 1966). Any nucleic acid molecule encoding a protein can be used to produce a protein, which can be used to produce an antibody, which can be used to detect the protein. However, to meet the requirements set forth under 35 USC § 101, a claimed invention must have a utility, which is specific to the substance and nature of the claimed subject matter.

Claims 47 and 51 recite that the claimed inventions can be used to diagnose a disease, or to determine if a subject is at risk for developing prostate cancer; however, for the reasons set forth in the previous Office action mailed November 26, 2003, this asserted utility is not specific and substantial. The specification asserts that the other claimed inventions might also be used to diagnose a disease, or to determine if a subject is at risk for developing prostate cancer. For the reasons set forth in the previous Office action, even given the benefit of Applicants' disclosure, the skilled artisan could not now use the claimed invention to diagnose the presence of a disease or to determine if a subject is at risk for developing prostate cancer.

All of the asserted utilities of the claimed invention that are disclosed in the specification are founded upon a presumption that the protein will be associated with the etiology of a disorder of cellular proliferation, such as prostate cancer. The inventor's presumption is entirely based upon data showing that the expression of an

antisense nucleic acid molecule in a breast cancer cell line blocks proliferative shutoff, which would normally occur following an androgen stimulated induction of cellular proliferation. However, the skilled artisan cannot predict whether the polypeptide of SEQ ID NO: 2 will be found associated with etiology of prostate cancer or any other disorder associated with abnormal cellular proliferation. The reasons are set forth below:

Regarding the possibility that the claimed invention might be useful, because the claimed nucleic acid molecules can be used to produce a polypeptide that is similar to AS3, i.e., the polypeptide of SEQ ID NO: 2, the skilled artisan cannot reliably or accurately predict the effects of amino acid sequence dissimilarities. Bowie et al. (*Science* 1990; **257**: 1306-1310) teaches that an amino acid sequence encodes a message that determines the shape and function of a protein; and, that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome. Bowie et al. also teaches that the prediction of protein structure from sequence data and, in turn, utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex (page 1306, column 1). Bowie et al. teaches that while it is known that many amino acid substitutions are possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three-dimensional structure/function relationship and these regions can tolerate only conservative substitutions or none at all (page 1306, column 2). Burgess et al. (*Journal of Cell Biology* 1990; **111**: 2129-2138) teaches the sensitivity of proteins to alterations of even a single amino acid in a sequence. This reference teaches that replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein. Lazar et al. (*Molecular and Cellular Biology* 1988; **8**: 1247-1252) teaches that a replacement of aspartic acid at position 47 with alanine or asparagine in transforming growth factor alpha had no effect but that a replacement with serine or glutamic acid sharply reduced its biological activity. The disclosures of

Burgess et al. and Lazar et al. teach that even a single amino acid substitution can often dramatically affect the biological activity and the structure-function characteristics of a protein. Thus, the function of a polypeptide cannot be predicted upon the basis of an observed sequence similarity to another protein; nor should the function of the polypeptide be reasonably expected to be the same as that of the other.

Additionally, regarding the possibility that the claimed invention might be useful, Skolnick et al. (*Trends in Biotechnology* 2000; **18**: 34-39) discloses that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate, in part because of the multifunctional nature of proteins (see, e.g., the abstract; and page 34, *Sequence-based approaches to function prediction*). Even in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein (see, in particular, the abstract and Box 2). Thus, one skilled in the art would not accept the assertion, which is based only upon an observed similarity in amino acid sequence, that an allelic variant of AS3 having at least 70% identity to the amino acid sequence set forth in SEQ ID NO: 2 is capable of being used in any specific and substantially beneficial manner, such as treating, preventing, or diagnosing a disorder or disease.

Regarding the possibility that the claimed invention might be diagnostically useful, Ward (*Developmental Oncology* 1985; **21**: 91-106) teaches not all markers can be reliably used in primary diagnosis. Ward teaches that a number of tumor-associated markers are, in fact, diagnostically unreliable. Rather, Ward teaches some markers are more useful as guides in monitoring the efficacy of treatment modules for malignant disease. Thus, even if data were presented showing that the abnormally expression of the polypeptide of SEQ ID NO: 2 correlates with the presence or incidence of a cellular disorder or disease, such data would not guarantee that that the claimed invention could be used in a specific manner to diagnose, for example, prostate cancer. Even if an altered level of expression of polypeptide of SEQ ID NO: 2 were found to be clinically significant, there is insufficient direction and guidance in the disclosure to enable the skilled artisan to use the claimed invention in a manner that could immediately benefit

the public. Tockman et al. (*Cancer Research* 1992; **52**: 2711s-2718s), for example, teaches many considerations that must be made in bringing a candidate tumor marker to successful clinical application; given only the benefit of Applicants' present disclosure, the skilled artisan could not use the claimed invention without having to perform additional experimentation of such complexity and measure that the public would not have derived any specific and substantial benefit from a grant of a patent monopoly of the existing information disclosed by Applicants.

Further regarding the field of DNA diagnostics, Critchfield (*Disease Markers* **15**: 108-111, 1999) teaches: "There is a process that occurs from the time that a gene is discovered until it has established clinical value. Indeed, to truly benefit society, the clinical value of the gene must be established" (page 109, column 1). Critchfield discusses the process of turning the discovery of a novel gene into demonstrated clinical value; and in view of Critchfield, given only the benefit of Applicant's present disclosure of the invention, it is apparent the skilled artisan could not immediately utilize the claimed invention in a manner that might benefit the public.

Finally, regarding the possibility that the claimed invention might be therapeutically useful, the art of drug discovery for is highly unpredictable. With regard to anticancer drug discovery, for example, Gura (*Science* 1997; **278**: 1041-1042) teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile (abstract). Gura teaches that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models, but that only 39 have actually been shown to be useful for chemotherapy (page 1041, first and second paragraphs). Moreover, because of the lack of predictability in the art, Gura discloses that often researchers merely succeed in developing a therapeutic agent that is useful for treating the animal or cell that has been used as a model, but which is ineffective in humans, indicating that the results acquired during pre-clinical studies are often non-correlative with the results acquired during clinical trials (page 1041, column 2).

Although the teachings of Bergers et al. (*Current Opinion in Genetics and Development* 2000; **10**: 120-127) are drawn to specific antitumor agents, namely matrix

metalloproteinase inhibitors, the great extent of unpredictability in the art is underscored by the disclosures of Berger et al. Bergers et al. teaches, "a body of data over the past few years indicate [...] that proteinases and proteinase inhibitors may, under special circumstance, either favor or block tumor progression. For example, ectopic expression of TIMP-1 [a natural inhibitor of metalloproteinases] allows for some tumors to grow, while inhibiting others" (page 125, column 2). In fact, Bergers et al., discloses that the Bayer Corporation recently halted a clinical trial of a metalloproteinase inhibitor because patients given the drug experienced greater progression of cancer than did patients given a placebo (page 125, column 1). Bergers et al. comments, "these results are somewhat surprising and contrary to Bayers' preclinical data, which confirmed that the drug inhibited tumor activity in rodents" (page 124, columns 1-2). The disclosure of Bergers et al. also teaches that the absence of a metalloproteinase activity in mice actually predisposes the mice to *de novo* squamous carcinomas. Thus, it is relatively clear that one skilled in the art cannot predict the effect of administering to a subject a pharmaceutical composition comprising an invention that is purported to have a desired pharmacological effect. Always the efficacy of any unproven drug regimen must be determined empirically. Therefore, in such an unpredictable art as this, because the disclosure is devoid of data generated by such empirical determinations, the skilled artisan would have to perform complex and lengthy courses of experimentation before the claimed invention might be used with any reasonable expectation of success to benefit the public.

For the reason set forth in section 10 of the Office action mailed November 26, 2001 (Paper No. 10), claims 47 and 51 had been previously rejected under 35 USC § 101, as lacking a specific and substantial asserted utility, a credible asserted utility, or a well-established utility. Applicants traversed this ground of rejection in Paper No. 12, arguing that the requirement set forth under 35 USC § 101 has been met by Applicants' disclosure of the claimed invention for the following reasons:

(a) At pages 84-86 the specification teaches AS3 is an androgen-induced suppressor of cell proliferation.

(b) AS3 is normally expressed at high levels in prostate cells, but in prostate cells evidencing uncontrolled growth or proliferation, such as prostate cancer cells that are not responsive to therapy, AS3 is expressed at comparably lower levels.

Additionally, Applicants have argued that the previous Office action mailed November 26, 2001 fails to provide a reasoned explanation as to why the asserted utilities are not specific, substantial, and credible. Applicants have asserted that it is unnecessary to provide evidence sufficient to establish that the claimed invention has a specific, substantial, and credible utility; moreover, Applicants have asserted that it is unnecessary to conduct a multi-centered epidemiological study to demonstrate the utility of the claimed invention.

Applicants' arguments have been carefully considered but not found persuasive for the following reasons:

Claim 51, for example, is drawn to a kit comprising a reagent that specifically detects an AS3 molecule, which is a nucleic acid that can selectively bind to a nucleic acid molecule encoding AS3, e.g., a probe. However, the generic usefulness of the claimed invention as a probe is not a specific utility because any nucleic acid molecule can be used as a probe to detect the presence of the same or another nucleic acid molecule comprising the polynucleotide sequence of the nucleic acid molecule.

Claim 51 recites that the claimed invention can be used to determine if a subject is at an increased risk of developing prostate cancer. This asserted utility, however, does not meet the requirements set forth under 35 USC § 101, because the asserted utility is not a specific and substantial utility, a credible utility, or a well-established utility.

To fulfill the requirements of 35 USC § 101, the Court has held an invention must have either an immediately obvious or fully disclosed "real world" utility. See *Brenner, Comr. Pats. v. Manson,* 148 U.S.P.Q. 689 (US SupCt, 1966).

Furthermore, the skilled artisan must be able to use a claimed invention in the manner asserted by Applicants' to provide some immediate benefit to the public. See *Nelson v. Bowler and Crossley*, 206 USPQ 881 (CCPA, 1980).

Given the benefit of Applicants' disclosure of the claimed invention, the skilled artisan could not now use the claimed invention to diagnose the presence of a disease

involving altered cell proliferation in a manner that would benefit the public; nor could the skilled artisan now use the claimed invention to determine that a subject has an increased likelihood of developing such a disease in a manner that would benefit the public. Moreover, the skilled artisan could not now use the claimed invention to determine if a subject is at increased risk for developing prostate cancer in a manner that would benefit the public. Before the invention cannot be used in a manner that immediately benefits the public, the skilled artisan would necessarily have to perform additional experimentation to elaborate upon Applicants' disclosed studies and determine firstly, whether the invention can be used in the real world to diagnose a disease or assess a subject's risk for developing a disease and secondly, how the invention can be used to diagnose a disease. Because the invention cannot be practiced in a manner that might immediately benefit the public, the requirements of 35 USC § 101 have not been met.

At page 82 the specification teaches that AS3 expression is a useful marker of responsiveness of a prostate cancer cell line to the inhibitory effects of androgens. However, contrary to Applicants' argument, the specification does not appear to disclose that AS3 is expressed at high levels in normal cells or that AS3 is under-expressed in prostate cancer cells or any other cells affected by a disease involving altered cell proliferation. Notably, the disclosure fails to establish a reasonable correlation between the level of expression of AS3 and the incidence, or risk for developing prostate cancer or any other disease involving altered cell proliferation.

Notably, the breadth of claim 47 includes any disease characterized by abnormal cellular proliferation and therefore includes diseases such as rheumatological diseases, including systemic lupus erythematosus (SLE), which is characterized by an abnormal proliferation of autoreactive lymphocytes, and diseases in which cellular proliferation is either up- or down-regulated. Certainly any "real world" utility of the claimed invention to diagnose a disease characterized by abnormal cellular proliferation, or assess a subject's risk for developing such a disease awaits further the investigation, as, for example, there is no evidence, or reasonable suggestion that AS3 can be used as a

diagnostic marker of SLE, or as a predictive marker for use in assessing a subject's risk for developing SLE.

Regarding the potential utility of the claimed invention to diagnose, or assess a subject's risk for developing prostate cancer, the Court has held that:

> The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility. Unless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field. Id., at 695.

Further, the Court has opined,

> [W]e are [not] blind to the prospect that what now seems without "use" may tomorrow command the grateful attention of the public. But a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion. Id., at 696.

While AS3 may eventually be found to be a useful biomarker of prostate cancer, or a risk thereofor, the claimed invention has not been refined and developed to a point, where the skilled artisan might use the claimed kits to diagnose prostate cancer, or to assess a subject's risk for developing prostate cancer. Again, the disclosure fails to establish a statistically and clinically significant correlation between the level of expression of AS3 and the incidence, or risk for developing prostate cancer or any other disease involving altered cell proliferation, and even if such a correlation were to be established or shown, the disclosure provides an insufficient amount of guidance to enable the skilled artisan to immediately use the claimed invention. For example, the specification fails to disclose the threshold level of AS3 expression that might be used to in a delineative fashion to definitively diagnose prostate cancer, or establish that a subject is more likely to develop prostate cancer than someone else.

Applicants have argued the previous Office action mailed November 26, 2001 fails to provide a reasoned explanation as to why the asserted utilities are not specific, substantial, and credible. The Examiner disagrees. The record, as a whole, indicates that the requirements of 35 USC § 101 have not been met by Applicants' disclosure of the claimed invention. A reasoned explanation as to why the asserted utilities of the claimed invention are not specific, substantial, and credible is provided by the Office

action mailed November 26, 2001 in section 15. The Office action establishes that even given the benefit of the disclosure, the skilled artisan could not practice the claimed invention with a reasonable expectation of success without the need to perform undue experimentation, which establishes that the claimed invention cannot now be used in a manner provided by Applicants to immediately benefit the public, as required by 35 USC § 101.

Claim Rejections - 35 USC § 112

13. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

14. Claims 1, 2, 4-12, 47-49, 51, and 68 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a credible asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

15. If Applicant were able to overcome the 35 USC § 112, first paragraph rejection above, claims 1, 2, 4-12, 47-49, 51, and 68 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the reasons set forth in section 13 of the previous Office action mailed November 26, 2001 (Paper No. 10).

Applicants have traversed this ground of rejection in Paper No. 12, arguing that the alleged differences in the sequences disclosed in GENBANK and the specification are only minor.

Applicants' arguments have been carefully considered but not found persuasive for the following reasons:

Applicants have disclosed and claimed a nucleic acid molecule encoding a protein designated AS3. The previous Office action incorrectly stated that there is only an 80.3% correspondence between the sequence set forth as SEQ ID NO: 1, which the specification discloses encodes AS3, and the sequence set forth as GENBANK Accession No. U95825, which is similarly disclosed by the Applicants to encode AS3. The sequences are actually 99.1% identical, but nonetheless there are twenty mismatches at positions throughout the alignment. As a result of these sequence differences, the sequences encode different polypeptides. It is unclear which sequence encodes AS3, or the disclosed invention.

To obviate this ground of rejection Applicants are asked to explain and/or resolve the discrepancy.

In addition, as noted in the objection above, the amino acid sequence encoded by SEQ ID NO: 3, the open reading frame of SEQ ID NO: 1, differs from the amino acid sequence set forth as SEQ ID NO: 2, which the specification teaches is the amino acid sequence encoded by SEQ ID NO: 3. As the disclosure fails to comply with the requirements set forth under 37 CFR §§ 1.821-1.825, correction of the apparent error in either SEQ ID NO: 2 or SEQ ID NO: 3, or some other satisfactory resolution of the apparent discrepancy in the teachings of the specification is required. Again, as stated above, it is noted that should the amino acid sequence of SEQ ID NO: 2 be incorrect, Applicants can resolve the discrepancy by altering the amino acid sequence of SEQ ID NO: 2 to accurately depict the amino acid sequence that is encoded by SEQ ID NO: 3.

It is noted that Applicants have additionally argued that the claimed invention would be more fully described and enabled upon submission of a deposit of the claimed biological material. It is agreed that deposit of the claimed biological material will obviate this ground of rejection, with the provision that the claims be amended to recite the ATCC deposit number of the deposited biological material and the deposit be perfected as required by current practices. See MPEP § 2400.

16. If Applicant were able to overcome the 35 USC § 112, first paragraph rejection above, claims 4-12 would still be rejected under 35 U.S.C. 112, first paragraph, because

the specification, while being enabling for an isolated nucleic acid molecule comprising the polynucleotide sequence set forth in SEQ ID NO: 1 or 3 or the full complement thereof, an isolated nucleic acid molecule comprising a fragment of at least 250 nucleotides of a nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO: 1 or SEQ ID NO: 3, wherein said fragment selectively hybridizes to a nucleic acid molecule encoding the polypeptide of SEQ ID NO: 2, an isolated nucleic acid molecule encoding a fragment of at least 15 contiguous amino acids of the amino acid sequence of SEQ ID NO: 2, wherein said fragment is capable of producing an antibody that binds specifically to the polypeptide of SEQ ID NO: 2, a vector comprising said nucleic acid molecule, a host cell comprising said vector, and a method for producing the polypeptide encoded by said nucleic acid molecule, does not reasonably provide enablement for an isolated nucleic acid molecule, which encodes a naturally occurring allelic variant of the polypeptide of SEQ ID NO: 2, or which encodes a polypeptide comprising an amino acid sequence at least about 70% identical to the amino acid sequence of SEQ ID NO: 2, or which hybridizes under recited stringent conditions to the nucleic acid of any one of claims 1, 2, 4, or 5, or any isolated nucleic acid molecule comprising a fragment of at least 250 nucleotides of a nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO: 1 or SEQ ID NO: 3, or any isolated nucleic acid molecule encoding a fragment of at least 15 contiguous amino acids of the amino acid sequence of SEQ ID NO: 2.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims for the reasons set forth in section 14 of the previous Office action mailed November 26, 2001 (Paper No. 10).

Applicants have traversed this ground of rejection in Paper No. 12, arguing that the specification provides ample guidance as to how one of skill in the art could make and use the claimed invention.

Applicants' arguments have been carefully considered but not found persuasive for the following reasons:

For the reasons set forth in the previous Office action, the skilled artisan cannot predict whether a polypeptide, which comprises an amino acid sequence that is different from the amino acid sequence of SEQ ID NO: 2, can be using in the same, or a similar manner as the polypeptide of SEQ ID NO: 2. The specification fails to teach how the polypeptides, which are encoded by the claimed nucleic acid molecules but do not have the function of the polypeptide of SEQ ID NO: 2, can be used. Therefore, the usefulness of a polypeptide that differs from the polypeptide of SEQ ID NO: 2, which is encoded by a polynucleotide sequence that is less than 100% identical to the polynucleotide sequence of SEQ ID NO: 3, would need to be determined empirically. Accordingly, unless the claimed nucleic acid molecule encodes a polypeptide that must retain a specific activity of the polypeptide of SEQ ID NO: 2, undue experimentation would need be performed to have a reasonable expectation of success in using the embodiments of the claimed invention, which do not encode a polypeptide comprising the amino acid sequence of SEQ ID NO: 2.

The skilled artisan cannot predict whether a polypeptide encoded by a nucleic acid molecule comprising a fragment of at least 250 nucleotides of a nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO: 1 or SEQ ID NO: 3, or the complement thereof, will have the function of the polypeptide of SEQ ID NO: 2. Similarly, the skilled artisan cannot predict whether a polypeptide encoded by a nucleic acid molecule encoding a fragment comprising at least 15 contiguous amino acids of SEQ ID NO: 2 will have the function of the polypeptide of SEQ ID NO: 2. Again, the specification fails to teach how the polypeptides, which are encoded by the claimed nucleic acid molecules but do not have the function of the polypeptide of SEQ ID NO: 2, can be used. Therefore, unless the claimed nucleic acid molecule comprising a fragment of SEQ ID NO: 1 or SEQ ID NO: 3 and the claimed nucleic acid molecule encoding a fragment comprising at least 15 contiguous amino acids of SEQ ID NO: 2, encode a polypeptide that must retain a specific activity of the polypeptide of SEQ ID NO: 2, or unless the claimed nucleic acid molecule encodes a polypeptide that can be used, for example, as an immunogen to produce an antibody that binds the polypeptide

of SEQ ID NO: 2, undue experimentation would need be performed to have a reasonable expectation of success in using the embodiments of the claimed invention.

Additionally, unless the claimed nucleic acid molecule that hybridizes under stringent conditions to the nucleic acid molecule of any one of claims 1, 2, 4, or 5 encodes a polypeptide that must retain a specific activity of the polypeptide of SEQ ID NO: 2, undue experimentation would need be performed to have a reasonable expectation of success in using these embodiments of the claimed invention.

For the reasons of record, the skilled artisan cannot predict whether a naturally occurring allelic variant of the polypeptide of SEQ ID NO: 2 will have the same, or even a similar function as the polypeptide of SEQ ID NO: 2. Accordingly, unless the claimed nucleic acid molecule a naturally occurring allelic variant of the polypeptide of SEQ ID NO: 2 encodes a polypeptide that must retain a specific activity of the polypeptide of SEQ ID NO: 2, undue experimentation would need be performed to have a reasonable expectation of success in using these embodiments of the claimed invention, because the skilled artisan would necessary have to elaborate a use for these embodiments.

It is noted that Applicants have argued that the specification discloses structural and functional features characteristic of AS3 family members, which presumably must comprise an amino acid sequence that is at least 70% identical to SEQ ID NO: 2, or be encoded by a polynucleotide sequence that is at least 70% identical to SEQ ID NO: 1 or SEQ ID NO: 3, as presently required by the claims. However, the disclosure does not establish a correlation between any particular element of the structure of the polypeptide of SEQ ID NO: 2 and any particular activity, which is specific to the polypeptide of SEQ ID NO: 2. For example, the specification discloses that the expression of an antisense molecule inhibits androgen-induced proliferation shutoff in STFX1 cells; however, the specification does not teach which of the characteristic structural elements of the AS3 family members is associated with the apparent growth suppressing activity of AS3, or the polypeptide of SEQ ID NO: 2. Accordingly, the skilled artisan could not predict whether a polypeptide encoded by an embodiment of the claimed invention has the same activity as the polypeptide of SEQ ID NO: 2, even given the sequence of the polypeptide, because it would not be known which region of

the amino acid sequence of the polypeptide of SEQ ID NO: 2 must be conserved in the amino acid sequence of the polypeptide so that the polypeptide retains the specific activity of the polypeptide of SEQ ID NO: 2. Moreover, the specification fails to disclose which amino acid residues must be retained in the structure of the polypeptides that differ from SEQ ID NO: 2, which are encoded by the claimed nucleic acid molecules, and by which other amino acids suitable replacements may be made, so that the polypeptides retain a specific activity of the polypeptide of SEQ ID NO: 2. Therefore, the specification provides an insufficient amount of guidance and direction to enable the skilled artisan to have a reasonable expectation of success in using the claimed invention in a manner specific to the nature of the invention.

Nevertheless, Applicants have argued that the specification teaches that the members of the family of AS3-like proteins can be identified by the presence of a DNA binding domain, a leucine zipper domain, and a kinase domain; however, it cannot be predicted which of these domains mediates the disclosed specific activity of AS3. For example, it might be argued that the members of the AS3 family of proteins are represented by AS3, i.e., the polypeptide of SEQ ID NO: 2, which has a DNA binding domain that binds to a consensus polynucleotide sequence, which is disclosed at page 79 of the specification, so that each member of the family must necessarily bind this polynucleotide sequence to retain a specific activity of AS3. The specification, however, discloses that NF-κB also binds to this sequence, or sequence similar thereto, and because NF-κB is not known to have the same specific activity of AS3 that is disclosed in the specification, namely the ability to suppress the androgen-induced growth of prostate cancer cells, it cannot be reasonably concluded that the members of the family of AS3 proteins, which do share the functional feature of binding to the consensus polynucleotide sequence, will also share the functional feature of suppressing the androgen-induced growth of prostate cancer cells. Accordingly, the specification fails to establish a correlation between a structural feature, which is purportedly shared by the polypeptides encoded by the different members of the claimed genus of nucleic acid

molecules, and a function feature, also common to at least a substantial number of the polypeptides.

Applicants have argued that only routine experimentation need be performed, so that the skilled artisan could make and use the claimed invention with a reasonable expectation of success, rather than an undue amount of experimentation. As explained, the specification does not teach how polypeptides, which differ from the polypeptide of SEQ ID NO: 2 and do not have a specific activity of the polypeptide of SEQ ID NO: 2, can be used; therefore, the skilled artisan would not know how to use the claimed nucleic acid molecules encoding these polypeptides. Additionally, as also explained, the specification does not teach how nucleic acid molecules that encode polypeptides that are less than 100% identical to SEQ ID NO: 2 *that suppress androgen-induced growth of prostate cancer cells* can be made. Therefore, the artisan would be left to manufacture each and every species of nucleic acid molecule, which comprises a polynucleotide sequence varying from the polynucleotide sequence of SEQ ID NO: 1 or SEQ ID NO: 3 by at most 30%, or which encodes a polypeptide having an amino acid sequence varying from the amino acid sequence set forth in SEQ ID NO: 2 by at most 30%, and then determine whether the polypeptide encoded by the nucleic acid molecules suppress androgen-induced growth of prostate cancer cells. Even allowing only one amino acid in a sequence the length of SEQ ID NO: 2, i.e., 182 amino acids, to vary, and limiting the variation to a deletion, insertion, or replacement, and limiting the pool of amino acids with which to make the insertion or replacement to those that are naturally occurring, the claims would encompass a genus of roughly 55,620 members; but the present claims allow for a substitution, insertion, or deletion at any number of positions up to about 417 to be made within the amino acid sequence of SEQ ID NO: 2, so the present claims encompass a still vast genus of polypeptides. Because one would reasonably imagine that the claims encompass many non-working embodiments, which could not be identified by any means other than producing a species of polypeptide comprising an amino acid sequence that is at least 70% identical to the amino acid sequence of SEQ ID NO: 2 and determining whether or not the species has

a specific activity of the polypeptide of SEQ ID NO: 2, finding the working embodiments among the possibilities would require undue experimentation.

17. If Applicant were able to overcome the 35 USC § 112, first paragraph rejection above, claim 10 would still be rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making and using an isolated host cell, does not reasonably provide enablement for any host cell encompassed by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claim 10 is drawn to a host cell comprising the vector of claim 6. Claim 10 is broadly interpreted to encompass host cells, which are not isolated and are comprised within an organism. Support for this interpretation of the claims can be found in the specification, e.g., at page 6, lines 6-8. Thus, the claims encompass host cells that have been transfected with the vector of claim 10 that are comprised within a transgenic animal, including nonhuman or human animals and animals treated using gene therapy.

The teachings of the specification cannot be extrapolated to the enablement of the claimed invention because the amount of guidance, direction, and exemplification set forth therein would not be sufficient to enable the skilled artisan to have a reasonable expectation of success in making and using the claimed invention without the need to perform additional, and an undue amount of experimentation. Factors to be considered in determining whether undue experimentation is required are summarized in *Ex parte Forman*, 230 USPQ 546 (BPAI 1986). These factors include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The specification does not provide a sufficient amount of guidance, direction, or exemplification to enable the skilled artisan to make or use host cells that are comprised

within a non-human transgenic animal. In the art of producing transgenic animals, the phenotype of the resultant transgenic animal is not always predicable or viable. Houdebine (*Journal of Biotechnology* 1994, **34**: 269-287) teaches the vectors to be used for directing the expression of transgenes in any given tissue, or in all tissues, must contain the appropriate regulatory regions. Houdebine teaches expression is heavily dependent on the site of integration in the host genome and the site of integration is presently unpredictable. Therefore, it is concluded that one of skill in the art would need to perform undue experimentation in order to make and use the claimed host comprised within a transgenic animal.

In addition, the specification does not teach provide a sufficient amount of guidance, direction, and exemplification to enable the skilled artisan to have a reasonable expectation of successfully producing host cells within a living organism, which comprise the vector of claim 10, by gene transfer, or *gene therapy*. The art of gene therapy, i.e., the *in vivo* delivery genetic information to targeted cells within a body using naked DNA or viral vectors or by reintroducing *ex vivo* modified host cells into the body, is still in its infancy. Moreover, the art is highly unpredictable and its successful application has been hindered by numerous limitations, which the specification does not remedy and would preclude the skilled artisan from having a reasonable expectation of successfully making and using the claimed invention without need of performing an undue amount of experimentation.

For example, the teachings of the specification have not overcome the problems with *in vivo* delivery and expression. Verma et al. (*Nature* 1997, **389**: 239-242) teach that the Achilles heel of gene therapy is gene delivery. Verma et al. state that the ongoing problem is the inability to deliver genes efficiently and to obtain sustained expression. Similarly, Amalfitano et al. (*Current Gene Therapy* 2002, **2**: 111-133) teach that non-viral mediated transfer of DNA generally suffers from low transduction efficiencies. In addition, Amalfitano et al. discuss numerous limitations that have been encountered in using retroviral vectors to deliver DNA into a subject and teach the use of adenoviral vectors can be ineffective because of the induction of strong immune

responses in the host to the viral vectors and direct acute and chronic toxicity caused by the vector itself.

It is noted that Amalfitano et al. teach that a despite general lack of success, the first conclusive evidence that gene therapy can show efficacy in humans was achieved in human X-linked SCID subjects *via* retrovirus transduction. However, since the publication, The Department of Health and Human Services has released a memorandum dated January 14, 2003, a copy of which is attached to this Office action, that urges all such investigations to be discontinued until new data are available, the possible etiology and risks of adverse events associated are considered, and recommendations emerge. Despite the initial promise of the trial studying gene transfer as a possible treatment for the disease, investigators have found that retroviral-mediated insertion of the transgene has caused the subjects to develop cancer. The results of the trial underscore the high degree of unpredictability associated with the art and the fact that the skilled artisan could not make or use the claimed invention with a reasonable expectation of success without need to perform additional experimentation.

The state of the art, as a whole, is well defined by Pandha et al. (*Current Opinion in Investigational Drugs* 2000; **1** (1): 122-134) in the abstract. Pandha et al. teach:

> Despite the rapid technological advances that continue to sustain the field of cancer gene therapy, few individual patients have benefited from the revolution so far. The plethora of clinical trials described confirms that each malignancy will have its own ideal strategy based on the associated molecular defects, and there has been rapid progress from this viewpoint. At the same time, there has been a renewed appreciation for the limitations to gene therapy, which include low efficiency of gene transfer, poor specificity of response and methods to accurately evaluate responses, and lack of truly tumor-specific targets at which to aim. As with all new therapies, we are climbing a steep learning curve in terms of encountering treatment-related toxicities, as well as profound ethical and regulatory issues.

In view of the preponderance of evidence establishing the state of the art, now and at the time the application was filed, and the level of unpredictability associated therewith, in the absence of a disclosure of an amount of guidance, direction, and exemplification that is reasonably commensurate in scope with the claims, it appears that skilled artisan could not make and use the claimed invention with a reasonable

expectation of success without having the need to perform an undue amount of experimentation.

Amending claim 11 to recite "isolated" before "host cell" can obviate this ground of rejection.

18. If Applicant were able to overcome the 35 USC §§ 101 and 112, first paragraph rejections above, claims 47 and 51 would still be rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the reasons set forth in section 15 of the previous Office action mailed November 26, 2001 (Paper No. 10).

Applicants have traversed this ground of rejection in Paper No. 12, arguing that the specification provides ample guidance as to how one of skill in the art could use the claimed invention.

Applicants' arguments have been carefully considered but not found persuasive for the following reasons:

The factors that have been considered in determining whether undue experimentation would be required to have a reasonable expectation of successfully using the claimed invention are summarized in *Ex parte Forman*, 230 USPQ 546 (BPAI 1986). These factors include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed. Applicants have remarked that patentability is not precluded by the necessity for some experimentation; however, the amount of experimentation that would need be performed so that the skilled artisan could have a reasonable expectation of successfully diagnosing, or assessing a subject's risk for developing prostate cancer, or some other disease involving altered cellular proliferation would be undue.

The use of the claimed invention has not been exemplified. The nature of the invention is such that to use the claimed invention with a reasonable expectation of success, the disclosure would have to teach the skilled artisan which diseases involving altered cellular proliferation can be diagnosed using the invention, and which cannot. As noted above, the claims encompass a kit for use in diagnosing a broad genus of diseases involving altered cellular proliferation, including, for example, SLE, but the skilled artisan could not use the claimed invention to diagnose SLE because there is no factual evidence suggesting the expression of AS3 is associated with the incidence of SLE. To the extent that the claims are drawn to a method for diagnosing, or assessing a subject's risk for developing prostate cancer, it is duly noted that the specification fails to teach what level of expression of AS3 in a suspected prostate cancer cell is indicative, or even suggestive of prostate cancer, and fails to teach what level of expression of AS3 in the normal prostate is associated with an increased risk for prostate cancer. Applicants have stated that AS3 is expressed in normal prostate cells and prostate cancer cells that are unresponsive to therapy, so the mere presence of messenger RNA (mRNA) encoding AS3 cannot be indicative of prostate cancer. Applicants' statements have suggested that the gene encoding AS3 is under-expressed in prostate cancer cells, but the threshold level of expression that delineates a prostate cancer cell from a normal prostate cell has not been disclosed; and the associated sensitivity and specificity of such a threshold cannot be predicted, or known without performing an undue amount of experimentation. The state of the art and the relative skill of those in the art is such that the level of AS3 expression that is reliably and accurately indicative of prostate cancer, or an increased risk for developing prostate cancer cannot be predicted and can only be determined empirically.

19. Claims 4-12 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In addition to the reasons set forth in section 16 of the previous Office action mailed November 26, 2001 (Paper No. 10), it is noted that claims 4 and 7 are drawn to a nucleic acid molecule, or a complement thereof, wherein said nucleic acid molecule encodes a naturally occurring allelic variant of a polypeptide comprising the amino acid sequence set forth as SEQ ID NO: 2. However, there is no factual evidence disclosed in the specification that would reasonably convey to the skilled artisan that Applicants had possession of a nucleic acid molecule encoding a naturally occurring allelic variant of the polypeptide of SEQ ID NO: 3.

Furthermore, it is noted that claims 5 and 7 encompass a large genus of nucleic acid molecules, or complements thereof, wherein said nucleic acid molecules comprise a polynucleotide sequence that is at least 70% identical to SEQ ID NO: 1 or SEQ ID NO: 3, or a complement thereof. The specification provides an adequate written description of a nucleic acid molecule comprising SEQ ID NO: 1, or the open reading frame thereof having the polynucleotide sequence of SEQ ID NO: 3. However, the specification does not provide adequate written description of the genus as a whole, because even given the benefit of Applicants' disclosure, the skilled artisan could not recognize at least a substantial number of the members of the claimed genus, or distinguish other nucleic acid molecules from those members.

Claims 5 and 7 encompass a large genus of nucleic acid molecules, or complements thereof, wherein said nucleic acid molecules comprise a fragment of at least 250 nucleotides of a nucleic acid molecule comprising SEQ ID NO: 1 or SEQ ID NO: 3. However, again, the specification does not provide adequate written description of the genus as a whole, because even given the benefit of Applicants' disclosure, the skilled artisan could not recognize at least a substantial number of the members of the claimed genus, or distinguish other nucleic acid molecules from those members.

Claims 5 and 7 also encompass a large genus of nucleic acid molecules, or complements thereof, wherein said nucleic acid molecule encodes a polypeptide that comprises an amino acid sequence that is at least 70% identical to the amino acid sequence of SEQ ID NO: 2. However, again, the specification does not provide adequate written description of the genus as a whole, because even given the benefit of

Applicants' disclosure, the skilled artisan could not recognize at least a substantial number of the members of the claimed genus, or distinguish other nucleic acid molecules from those members.

Claim 6 encompasses a large genus of nucleic acid molecules that are capable of hybridizing to a nucleic acid molecule of any one of claims 1, 2, 4, and 5 under recited conditions. However, again, the specification does not provide adequate written description of the genus as a whole, because even given the benefit of Applicants' disclosure, the skilled artisan could not recognize at least a substantial number of the members of the claimed genus, or distinguish other nucleic acid molecules from those members.

In Paper No. 12, Applicants traversed the rejection of claims 4-12 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the reasons set forth in section 16 of the previous Office action mailed November 26, 2001 (Paper No. 10). Applicants argued that the specification discloses a structural feature common to at least a substantial number of the polypeptides encoded by the claimed genus of nucleic acid molecules, and therefore meets the written description requirements set forth under 35 USC § 112, first paragraph. Again, Applicants point to the disclosure that the AS3 polypeptide of SEQ ID NO: 2 has a DNA binding domain, a putative leucine zipper domain, and a putative kinase domain. Applicants have argued that the claims are not drawn to any and all nucleic acid molecules encoding a protein, only to those nucleic acid molecules that hybridize to the complement of a nucleic acid molecule comprising the polynucleotide sequence of SEQ ID NO: 1 or SEQ ID NO: 3 under stringent hybridization conditions. Additionally, Applicants have argued that the specification teaches how the claimed genus of nucleic acid molecules encoding an allelic variant of the polypeptide of SEQ ID NO: 2 can be made, or isolated.

Applicants' arguments have been carefully considered but not found persuasive for the following reasons:

It is agreed that the Court indicated that while Applicants are not required to disclose every species encompassed by a genus, an adequate written description of a genus may achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. See *The Reagents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412). However, the specification does not disclose distinguishing and identifying features of a representative number of members of the genus of polypeptides to which the claims are drawn, such as a correlation between the structure of the polypeptide of SEQ ID NO: 2 and its recited function, so that the skilled artisan could immediately envision, or recognize at least a substantial number of members of the claimed genus of compositions. Moreover, the specification fails to disclose which amino acid residues are essential to the function of the polypeptide of SEQ ID NO: 2, or which amino acids might be replaced or deleted so that the resultant polypeptide retains the activity of its parent, or by which other amino acids the essential amino acids might be replaced so that the resultant polypeptide retains the activity of its parent. Therefore, the specification fails to adequately describe at least a substantial number of members of the claimed genus of compositions comprising polypeptides that differ from the polypeptide of SEQ ID NO: 2.

The Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, paragraph 1, ``Written Description'' Requirement (66 FR 1099-1111, January 5, 2001) state, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (*Id.* at 1104). Moreover, because the claims encompass a genus of variant species, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. However, factual evidence of an actual

reduction to practice has not been disclosed by Applicant in the specification; nor has Applicant shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; nor has Applicant described distinguishing identifying characteristics sufficient to show that Applicant were in possession of the claimed invention at the time the application was filed.

Furthermore, the art is unpredictable, and the *Guidelines* state, "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species *cannot* be achieved by disclosing only one species within the genus" (Id. at 1106); accordingly, it follows that an adequate written description of the claimed genus cannot be achieved in the absence of a disclosure of a substantial, or at least a representative number of species within the genus.

In reply to Applicants' argument that that the claims are not drawn to any and all nucleic acid molecules encoding a protein, only to those nucleic acid molecules that hybridize to the complement of a nucleic acid molecule comprising the polynucleotide sequence of SEQ ID NO: 1 or SEQ ID NO: 3 under stringent hybridization conditions, in *The Reagents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the Court held that a generic statement that defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. Presently claim 6 requires the nucleic acid molecule to hybridize under stringent conditions to the nucleic acid molecule of any one of claims 1, 2, 4, or 5, but this is merely a recitation of what the nucleic acid molecule must do, not what the nucleic acid molecule is.

In reply to Applicants' argument that the specification teaches how the claimed genus of nucleic acid molecules encoding an allelic variant of the polypeptide of SEQ ID NO: 2 can be made, or isolated, MPEP § 2163.02 states, "[a]n objective standard for determining compliance with the written description requirement is, 'does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed' ". The courts have decided:

> The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed*.

See *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Federal Circuit, 1991). Furthermore, the written description provision of 35 USC § 112 is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.,* 18 USPQ2d 1016 (CAFC 1991). Finally, tThe Court has decided, "[a]n adequate written description of a DNA [molecule] 'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention". See *The Reagents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412).

In summary, the specification fails to describe any structural or functional characteristic or essential common feature of the members of claimed genus of proteins, which would serve to distinguish these two proteins and the other members of the claimed genus from proteins that are not claimed. The skilled artisan could not envision the structures of the members of the claimed genus that have not been described in the specification and therefore, the member that is described is not considered representative of the genus as a whole.

20. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

21. Claims 47 and 51 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for the reasons set forth in section 18 of the previous Office action mailed November 26, 2001 (Paper No. 10).

Applicants have traversed this ground of rejection in Paper No. 12, arguing the specification provides several examples of cell lines and describe the degree of

alteration in cell proliferation that can be observed, so that claim 47 is not indefinite under 35 USC § 112, second paragraph. Again, regarding claim 47, Applicants have asserted that the term "increased likelihood" is sufficiently definite that the skilled artisan would be reasonably apprised of the metes and bounds of the claim. Regarding claim 51, Applicants have similarly argued the terms "at increased risk" and "reduced [...] levels of AS3" are sufficiently definite that the skilled artisan would be reasonably apprised of the metes and bounds of the claim; and Applicants have asserted that it would be readily apparent which necessary control would need to be used to establish a standard for determining the requisite degree of increased risk, or reduced expression.

Applicants' arguments have been carefully considered but not found persuasive for the following reasons:

Claim 47 is vague and indefinite because the claim recites the phrase "a disease involving *altered* cell proliferation" (italicized for emphasis). As set forth in the previous Office action, it is unclear relative to what standard the claim requires the proliferation of the cell(s) to be altered. Applicants have argued that the specification provides several examples of cell lines and describe the degree of alteration in cell proliferation that can be observed; however, since, for example, it is unclear whether the recited disease involves increased, or decreased cell proliferation, it would be unclear which, if any of the disclosed cell lines could and should serve as a standard in practicing the claimed method. Furthermore, Applicants are reminded that limitations cannot be read into the claims. Accordingly, amending claim 47 to recite how cell proliferation must be altered, and to what extent, relative to a particular control, can obviate this ground of rejection.

Claim 47 is also vague and indefinite because the claim recites the phrase "an increased likelihood". As set forth in the previous Office action, the term "increased" is a relative term. Because it is not clear to what standard the likelihood that the mammal will develop the disease is to be compared, the metes and bounds of the subject matter encompassed by the claim is not sufficiently delineated to meet the requirements of 35 USC §112, second paragraph. Amending claim 47 to recite a standard relative to which the determination of the increased likelihood can be made can obviate this ground of rejection. Similarly, claim 51 is vague and indefinite because the claim recites the terms

"at increased risk" and "reduced [...] levels of AS3". Amending claim 51 to recite standards relative to which the determination of the increased risk, or reduced levels of AS3 can be made can obviate this ground of rejection.

Claim Rejections - 35 USC § 102

22. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

23. Claims 5-12, 47, and 51 are rejected under 35 U.S.C. 102(a) as being anticipated by Geck, et al (*Journal of Steroid Biochemistry and Molecular Biology* **68**: 41-50, 1999).

Geck et al. (1999) teaches that which is set forth in section 20 of the previous Office action mailed November 26, 2001 (Paper No. 10). In addition, it is duly noted that Geck et al. discloses a fusion protein of AS3 and GST at page 49.

Applicants have traversed this ground of rejection in Paper No. 12, arguing that Geck et al. (1999) represents Applicants own work, published within the year before the filing date of the present application, and is not prior art under 35 USC § 102(a).

Applicants' arguments have been carefully considered but not found persuasive for the following reasons:

Geck et al. (1999) is not authored by the inventive entity that filed the present application. Geck et al. (1999) is a disclosure of the claimed invention by another, which was published before the filing date of the present application and therefore is properly regarded as prior art under 35 USC § 102(a).

24. Claims 5-7, 9-11, 47, and 51 are rejected under 35 U.S.C. 102(b) as being anticipated by Geck, et al (*Journal of Steroid Biochemistry and Molecular Biology* **63**:

211-218, 1997) for the reasons set forth in section 21 of the previous Office action mailed November 26, 2001 (Paper No. 10).

Applicants have traversed this ground of rejection in Paper No. 12, arguing that the prior art is not enabling because it fails to teach the polynucleotide sequence of the nucleic acid molecule, and to anticipate a claimed invention, the prior art must teach each and every element of the claimed invention.

Applicants' arguments have been carefully considered but not found persuasive for the following reasons:

The prior art does teaches the polynucleotide sequence of the isolated nucleic acid molecule. However, the prior art teaches how the AS3 encoding nucleic acid molecule can be made. Thus, the prior art provides an enabling disclosure of an isolated nucleic acid molecule encoding AS3.

Although the prior art does not explicitly teach the polynucleotide sequence of the isolated AS3 encoding nucleic acid molecule, the polynucleotide sequence of the molecule is an inherent property of the molecule. It is duly noted that GenBank™ Accession No. U95825 is annotated to provide evidence that the nucleic acid molecule disclosed therein is the same as the nucleic acid molecule isolated and disclosed by the prior art. The polynucleotide sequence of the isolated nucleic acid molecule of the prior art is 99.1% identical to the polynucleotide sequence set forth as SEQ ID NO: 1.

Accordingly, the nucleic acid molecule of the prior art is deemed the same as the claimed nucleic acid molecule, absent a showing of any difference. However, the Office does not have the facilities for examining and comparing Applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural, and functional characteristics as the claimed nucleic acid. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed nucleic acid molecule is different than any taught by the prior art. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA, 1977) and *Ex parte Gray*, 10 USPQ2d 1922 1923 (PTO Board of Patent Appeals and Interferences, 1988 and 1989).

25. Claims 5-7, 9, 47, and 51 are rejected under 35 U.S.C. 102(b) as being anticipated by GenBank™ Accession No. U50533 (27 November 1996) for the reasons set forth in section 23 of the previous Office action mailed November 26, 2001 (Paper No. 10).

Applicants have traversed this ground of rejection in Paper No. 12, arguing that the prior art fails to anticipate the claimed invention, because the prior art fails to disclose any polypeptide sequence or ascribe any function to the polynucleotide sequence.

Applicants' arguments have been carefully considered but not found persuasive for the following reasons:

Claim 5 is drawn to a nucleic acid molecule that encodes a fragment of a polypeptide of the amino acid sequence of SEQ ID NO: 2, limiting the term "fragment" by reciting, "wherein the fragment comprises at least 15 contiguous amino acid residues of the amino acid sequence of SEQ ID NO: 2". Claim 5 is interpreted to encompass any nucleic acid molecule encoding a fragment of a polypeptide that comprises at least 15 contiguous amino acid residues of SEQ ID NO: 2, not just a nucleic acid molecule encoding a fragment of the polypeptide of SEQ ID NO: 2. The polynucleotide sequence of the isolated nucleic acid molecule of the prior art comprises a nucleotide sequence that encodes a fragment of a polypeptide comprising the amino acid sequence of SEQ ID NO: 2, which fragment comprises at least 15 contiguous amino acid residues of SEQ ID NO: 2. Accordingly, the prior art is deemed to anticipate the claimed invention. It is not necessary that the prior art disclose, or ascribe the function of the fragment of a polypeptide encoded by the polynucleotide sequence of the disclosed nucleic acid molecule, because claim 5 does not recite a limitation requiring the fragment of a polypeptide to have any particular function or characteristic, apart from comprising at least 15 amino acid residues of SEQ ID NO: 2.

26. Claim 47 is rejected under 35 U.S.C. 102(b) as being anticipated by Promega™ 1993/1994 Biological Research Products Catalog.

Claim 47 is drawn to a material for measuring AS3 RNA, which is contained and included in a kit. The recitation of intended use in the preamble of the claim has not given weight in comparing the product of the prior art and the claimed product.

The prior art discloses a kit comprising a material for measuring RNA; although the catalog does not expressly disclose that the material can be used to measure RNA encoding AS3, the product of the prior art is deemed the same as the product of the claims, absent a showing of any difference, because it is fully and reasonably expected that the material of the kit of the prior art can be used to measuring RNA encoding AS3.

27. Claim 51 is rejected under 35 U.S.C. 102(b) as being anticipated by Boehringer Mannheim 1994 Catalog, Biochemicals (No. 1034 731/1006 924).

Claim 51 is drawn to at least one reagent, which is contained and included in a kit, wherein said reagent is a nucleic acid molecule that can selectively bind to a nucleic acid molecule encoding AS3. The recitation of intended use in the preamble of the claim has not given weight in comparing the product of the prior art and the claimed product. Similarly, the recitation that the kit comprises instructions has not given any weight.

The prior art teaches a kit comprising random primers that encompass all possible 6-nucleotide sequences. The kit therefore comprises an isolated nucleic acid molecule that can selectively bind to a nucleic acid molecule encoding AS3.

Claim Rejections - 35 USC § 103

28. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

29. Claims 5-12, 47, 49, and 51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Geck, et al (*Journal of Steroid Biochemistry and Molecular Biology* **63**: 211-218, 1997).

Geck et al. (1999) teaches that which is set forth in sections 20 and 27 of the previous Office action mailed November 26, 2001 (Paper No. 10).

Geck et al. (1999) teaches providing a cell comprising a nucleic acid molecule that encodes the AS3 polypeptide; in addition, Geck et al. (1999) teaches a method for isolating cDNA molecules encoding AS3 polypeptide, wherein said method comprises amplifying the cDNA molecules by PCR using primers that are greater than 15 nucleotides in length, which can optionally comprise sequences capable of producing restriction endonuclease cut sites in the amplified product.

However, Geck et al. (1999) does not expressly teach that the AS3 polypeptide can be *isolated*, as recited in claim 48. Furthermore, Geck et al. (1999) does not expressly teach a process for isolating *a genomic DNA molecule or portion thereof* that comprises PCR amplification of the DNA molecule or portion thereof.

It would have been *prima facie* obvious to one of ordinary skill in the art given the teachings of Geck et al. (1999) that a genomic DNA molecule or a portion thereof can be isolated by a process comprising amplifying the DNA molecule or portion thereof by PCR using primers, which are greater than 15 nucleotides in length. One of ordinary skill in the art at the time the invention was made would have been motivated to amplify a genomic DNA molecule, or portion thereof, which encodes the AS3 polypeptide, to obtain an isolated genomic DNA molecule or portion thereof encoding the AS3 polypeptide.

30. Claim 48 is rejected under 35 U.S.C. 103(a) as being unpatentable over Geck et al. (*Journal of Steroid Biochemistry and Molecular Biology* **68**: 41-50, 1999) as applied to claims 5-12, 47, 49, and 51 above, and further in view of Bendig (*Genetic Engineering* **7**: 91-127, 1988).

Geck et al. (1999) teaches that which is set forth in the rejection above.

Geck et al. (1999) teaches providing a cell comprising a nucleic acid molecule that encodes the AS3 polypeptide; and Geck et al. teaches culturing the cell under conditions appropriate for expressing the nucleic acid molecule.

However, Geck et al. (1999) does not expressly teach that the AS3 polypeptide can be *isolated*, as recited in claim 48.

Bendig reviews the art of producing proteins in mammalian cells by processes that comprise providing a cell comprising a nucleic acid molecule that encodes a protein, culturing the cell under conditions appropriate for expressing the nucleic acid molecule, and subsequently isolating the protein encoded by the nucleic acid molecule.

Given the state of the art, as reviewed by Bendig, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use an expression vector comprising the isolated cDNA molecule of Geck et al. (1999), which encodes the AS3 polypeptide, to obtain the AS3 polypeptide by a process comprising culturing host cells transfected with the expression vector under conditions that are appropriate for expression of the cDNA molecule to produce the protein and isolating the protein so produced. The methodology was conventional and routine. One of ordinary skill in the art at the time the invention was made would have been motivated to obtain the AS3 polypeptide, for example, to use the polypeptide to produce an reagent antibody that binds specifically to the AS3 polypeptide to facilitate additional studies designed to further elucidate the biologic function of the AS3 polypeptide.

31. Claims 5-12, 47, 48, and 51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Geck, et al (*Journal of Steroid Biochemistry and Molecular Biology* **63**: 211-218, 1997), as evidenced by GENBANK Accession No. U95825, in view of Knappik et al. *(Biotechniques* **17**: 754-761, 1994).

Geck et al. (1997) teaches that which is set forth in sections 21 and 28 of the previous Office action mailed November 26, 2001 (Paper No. 10).

As evidenced by the annotation of GENBANK Accession No. U95825, Geck et al. (1997) teach a nucleic acid molecule comprising a polynucleotide sequence that encodes the AS3 polypeptide.

Geck et al. (1997) do not expressly teach or suggest a nucleic acid molecule encoding a fusion protein comprising a polynucleotide sequence encoding the AS3 polypeptide and further comprising a polynucleotide sequence encoding a heterologous polypeptide. Furthermore, Geck et al. do not expressly teach or suggest isolating an AS3 polypeptide after culturing a host cell comprising a nucleic acid molecule encoding the polypeptide under conditions appropriate for its expression.

Knappik et al. teach the utility of producing a recombinant DNA molecule encoding a fusion protein comprising a polynucleotide sequence encoding a polypeptide of interest and further comprising a polynucleotide sequence encoding a heterologous polypeptide, namely the FLAG affinity tag. Knappik et al. discloses that the FLAG affinity tag is a versatile tool for both sensitive detection and one-step purification of recombinant proteins.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have to use an expression vector comprising the isolated cDNA molecule of Geck et al., which encodes the AS3 polypeptide, and a nucleic acid comprising a heterologous polypeptide, namely the FLAG affinity tag to obtain a fusion protein comprising AS3 and the FLAG affinity tag by a process of culturing host cells transfected with the expression vector under conditions that are appropriate for expression of the nucleic acid molecule to produce the fusion protein and isolating the fusion protein so produced, because such methodology was conventional and routine. One of ordinary skill in the art at the time the invention was made would have been motivated to make the expression vector encoding the fusion protein comprising AS3 and the FLAG epitope, because antibodies that bind specifically to the FLAG epitope were commercially available and could be used to immunoprecipitate the fusion protein to facilitate its isolation and purification. One of ordinary skill in the art at the time the invention was made would have been motivated to thus obtain the fusion protein comprising the amino acid sequence of the AS3 polypeptide and the FLAG epitope to facilitate one-step purification; one of ordinary skill in the art at the time the invention was made would have been motivated to purify the fusion protein to use the protein, for example, as an immunogen in the process of

producing a reagent antibody that binds specifically to the AS3 polypeptide for additional studies designed to further elucidate the biologic function of the AS3 polypeptide.

Response to Applicants' Remarks

32. In Paper No. 12, Applicants have traversed the rejection of claims 1, 2, 5-12, 47-49, and 51 under 35 U.S.C. 103(a) as being unpatentable over Geck, et al (*Journal of Steroid Biochemistry and Molecular Biology* **68**: 41-50, 1999) for the reasons set forth in section 27 of the previous Office action mailed November 26, 2001 (Paper No. 10). This rejection has been withdrawn in favor of the rejection set forth above; nevertheless, Applicants' remarks have been considered below.

Applicants argued that Geck et al. represents Applicants own work, published within the year before the filing date of the present application, and is not prior art under 35 USC § 103.

Applicants' arguments have been carefully considered but not found persuasive for the following reasons:

Geck et al. is not authored by the inventive entity that filed the present application. Geck et al. is a disclosure of the claimed invention by another, which was published before the filing date of the present application and therefore is properly regarded as prior art under 35 USC § 103 in accordance with 35 USC § 102(a).

33. In Paper No. 12, Applicants have traversed the rejection of claims 5-12, 47-49, and 51 under 35 U.S.C. 103(a), as being unpatentable over Geck, et al (*Journal of Steroid Biochemistry and Molecular Biology* **63**: 211-218, 1997) for the reasons set forth in section 28 of the previous Office action mailed November 26, 2001 (Paper No. 10). This rejection has been withdrawn in favor of the rejection set forth above; nevertheless, Applicants' remarks have been considered below.

Applicants argued that the skilled artisan would not have known which open reading frame to use in order to express the AS3 polypeptide as a fusion protein.

Applicants' arguments have been carefully considered but not found persuasive. In reply to Applicants' argument that the skilled artisan would not have known which open reading frame to produce a fusion of the polypeptide of SEQ ID NO: 2 and the FLAG epitope, it is duly noted that claim 8 is not limited to a nucleic acid molecule encoding a fusion polypeptide comprising SEQ ID NO: 2 and the amino acid sequence of the FLAG epitope. Nevertheless, given the teachings of the prior art, it would have been obvious and routine to deduce the amino acid sequence that is encoded by the polynucleotide sequence of the isolated nucleic acid molecule, and one would have been motivated to do so in view of the teachings of Geck et al., because Geck et al. teach the desirability of characterizing the polypeptide encoded by the isolated nucleic acid molecule, which polypeptide Geck et al. discloses mediates proliferative shutoff in prostate cancer cells following androgen-induced proliferation. Then, as set forth in the previous Office action, it would have been obvious to produce and use an expression vector comprising the isolated cDNA molecule of Geck et al., which encodes AS3, and a nucleic acid comprising a heterologous polypeptide, namely the FLAG epitope to obtain a fusion protein comprising AS3 and the FLAG epitope by a process of culturing host cells transfected with the expression vector under conditions that are appropriate for expression of the nucleic acid molecule to produce the fusion protein and isolating the fusion protein so produced, because such methodology was conventional and routine. One of ordinary skill in the art would have known that the polynucleotide sequence encoding the polypeptide, which is encoded by the polynucleotide sequence of the nucleic acid of Geck et al., and the polynucleotide sequence encoding the FLAG epitope have to be in the same translation frame, if the expression vector is to be used to produce the desired fusion protein. As stated in the previous Office action, one of ordinary skill in the art at the time the invention was made would have been motivated to make the expression vector encoding the fusion protein comprising AS3 and the FLAG epitope, because antibodies that bind specifically to the FLAG epitope were commercially available and could be used to immunoprecipitate the fusion protein to facilitate its isolation and purification. One of ordinary skill in the art at the time the invention was made would have been motivated to thus obtain the fusion protein

comprising AS3 and the FLAG epitope for use in producing a reagent antibody that binds specifically to AS3 for additional studies designed to further elucidate the biologic function of AS3.

Conclusion

34. No claims are allowed.

35. The art made of record and not relied upon is considered pertinent to Applicants' disclosure. Terpe et al. reviews the utility of tag fusion proteins, including FLAG-tag fusion proteins.

36. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (703) 305-3008. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony C. Caputa, Ph.D. can be reached on (703) 308-3995. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1642

slr
December 15, 2003

Notice to Comply	Application No.	Applicant(s)	
	09/512,581	SOTO ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1642	

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☒ 7. Other: The amino acid sequence encoded by SEQ ID NO: 3 is not SEQ ID NO: 2; because the disclosure teaches that SEQ ID NO: 3 encodes SEQ ID NO: 2, the specification fails to comply with the requirments set forth under 37 CFR 1.821-1.825. If necessary to correct the deficiency, Applicants should submit substitute copies of the sequence listing and a statement, as indicated below.

Applicant Must Provide:

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☒ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216
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